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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,223	03/09/2001	Robert Korngold	KOR01-NP002	6791

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,223	KORNGOLD ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5,6 and 8-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and remarks, filed 8/29/03, has been entered.

2. Claims 2, 3, 5, 6, 8-11, and newly added Claims 12-14, are pending and being acted upon.

3. In view of Applicant's amendment, all previous rejections under the first paragraph of 35 U.S.C. 112 have been withdrawn.

4. Applicant continues to traverse the denial of the benefit of priority to U.S. Provisional Application No. 60/188,391. "Applicants assert that, contrary to the Examiner's allegation that "inhibit" has a broader meaning than "prevent" because it is defined as "retard or prevent" the definition should be interpreted to mean that the terms are interchangeable based on the context in which they are used. Both terms are used throughout the pending specification as filed, and the term "prevent" was used throughout provisional application '391."

It remains the Examiner's position that "to inhibit" has a broader definition than "to prevent". There is no evidence of record to support Applicant's assertion that Applicant intended "to prevent" to include "to inhibit" in the provisional application, or that Applicant intended "to inhibit" to be limited to "to prevent" in the instant application.

Applicant argues "[The] 391 [application] describes the use of two different populations of cells derived from a population of hematopoietic stem cells (HSC), namely from PBMCS. Although '391 does not specifically recite the act of "separating" the cells, the act is implied in using the two populations or fractions of cells, and one of ordinary skill in the art would understand that the act of separating the cells would be required to obtain the two fractions of cells from the parent HSC population."

It remains the Examiner's position that the disclosure at page 2 of the '391 application indicates a separation step involving PBMC and fails to disclose a step involving hematopoietic stem cells. Just as obviousness is not the standard for the introduction of new matter, it cannot be the standard for the granting of priority. The granting of priority to claims that could not be supported by the parent application would be essentially equivalent to the allowing of the introduction of new matter into the parent. Accordingly, the denial of priority to Claims 2, 3, 5, 6, 8-11 is again deemed proper.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 2, 3 and 5, 6, 8-11, and newly added Claims 12-14 stand/are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenfeld et al. (1995, IDS) in view of Small et al. (1999, IDS) and U.S. Patent No. 5,668,112 (1997, IDS), for the reasons of record as set forth in Paper No. 10, mailed 3/27/03.

Applicant's arguments, filed 8/29/03, have been fully considered but they are not persuasive. Applicant argues, "Rosenfeld, combined with Small and '112, does not teach or suggest all of the claimed elements of the present invention. First, Rosenfeld teaches treating bone marrow with LLME to eliminate cytotoxic T cells (see abstract) prior to transplantation and does not teach or suggest treating donor lymphocytes with LLME for infusion after allogeneic T cell-depleted hematopoietic stem cell transplantation, as claimed in independent claims 2, 3, or 5, or new independent claims 12, 13, and 14."

It is the Examiner's position that while Rosenfeld et al. teaches the treating of bone marrow (rather than lymphocytes) with LLME, the reference also teaches the problem with the method (progenitor and CFU cell toxicity) that is solved by the method of the combined references. Thus, rather than teach away from the claimed method, Rosenfeld et al. simply teaches that the method can be improved.

Applicant argues "The patients in Rosenfeld do not meet the limitation of claim 1, "a mammal in need of DLI," just because they had received total body irradiation. Subsequent to radiation, the patients in Rosenfeld received only a bone marrow transplant, not DLI."

It is the Examiner's position that the problems of bone marrow transplantation alone were well known at the time (see, for example the Background of the Invention section of the instant application). Clearly, DLI after bone marrow transplantation was known at the time of the invention to be needed by most, if not all, bone marrow transplant patients.

Applicant argues that Rosenfeld et al. does not teach the dosages and timing of the amended claims.

It is the Examiner's position that the optimization of dosage and timing were well within the purview of one of skill in the art at the time of the invention and were therefor obvious.

Applicant argues that given certain teachings regarding "class 2 discrepancies", the combined references would not have been expected to provide an effective method for the prevention of GVHD.

It is the Examiner's position that it was well known in the art that granulated killer cells (CTL and NK) were major contributors to GVHD. It was also well known that LLME treatment could reduce the number of said cells. Accordingly, the method of the instant claims was obvious in view of the prior art and what one of skill in the art would have known at the time of the invention. Regarding an expectation of success, it remains the Examiner's position that the removal of granulated killer cells was well known to be of benefit to transplant patients and there existed every likelihood that the treatment would have been successful.

Applicant argues "Contrary to the assertion of the Examiner, the '112 patent does not teach that NK cells and cytotoxic cells are primarily responsible for GVHD after DLI. Instead, '112 teaches that [s]ince cytotoxic T cells (CTL) derived from donor bone marrow appear to be the final mediators of GVHD, in vitro treatment of donor bone marrow with an agent which selectively damages cytotoxic T cell precursors is also likely to be of benefit."

Clearly the reference *does* actually teach that NK and CTL are mediators of GVHD. When combined with the additional references the method of the instant claims is rendered obvious.

Applicant argues further argues a lack of motivation to combine the references. Specifically, Applicant argues a lack of motivation to combine the references and result in each of the individual steps. As part of this argument Applicant includes numerous arguments that involve unclaimed limitations, i.e., "Neither Small nor Rosenfeld teach or suggest that infusing LLME treated cells after hematopoietic stem cell transplantation or engraftment induces or accelerates recovery of CD4+ cells," and "There would have been no motivation to use LLME treated donor lymphocytes to ward off opportunistic infection."

Applicant is advised that arguments regarding unclaimed limitations lend little support to the patentability of the method of the instant claims. It is the Examiner's position that the motivation to combine the references need not be that of the instant Inventors.

Applicant argues "Rosenfeld, Small, and '112, when combined, do not teach or suggest separating cells into CD34+ (stem cell) and CD34- (nonstem cell) fractions before LLME treatment, as claimed in claims 5 and 14."

It is noted that Rosenfeld et al. teaches "allogeneic stem cell transplantation," thus, it is the Examiner's position that some separation step would have been obvious.

As set forth in MPEP 2144:
"The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983)."

Given the motivation to improve the methods of the prior art, in view of what would have been known to one of skill in the art at the time of the invention, it remains the Examiner's position that the claimed invention, for the reasons set forth previously, would have been obvious to one of skill in the art at the time of the invention.

7. The following are new grounds of rejection.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 9 and 10 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) The phrase, "therapeutically effective amount of L-leucyl-L-leucine methyl ester is 375 micromolar", in Claim 9, comprises a limitation not supported by the specification or claims as filed.

B) The phrase, "contact is for 15 minutes" in Claim 10, comprises a limitation not supported by the specification or claims as filed.

Applicant is advised that this specific dosage and time is found only in the single example disclosed in the specification. This example does not encompass all of the more generic embodiments of the instant claims. Accordingly, the specific limitations of the example could only be claimed in claims reciting the specific method in which they are disclosed. It is improper to recite the specific limitations in broader generic claims.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973.

Please Note: inquiries of a general nature or relating to the status of this application should not be directed to the Examiner but rather should be directed to the Technology Center 1600 Customer Service Center at (703) 308-0198.

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600
November 28, 2003

11/28/03
G.R. EWOLDT, PH.D.
PRIMARY EXAMINER